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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,575	11/28/2000	Dale B. Schenk	15270-005912	6096

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,575	SCHENK, DALE B.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,58 and 74-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,58 and 74-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks, amendments, and declaration filed 21 February 2006 have been entered. Claims 11, 58, and 74 – 81 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. Applicant has amended the fist line of the specification in the present amendment. According to the newly-filed information, the instant application is a continuation of 09/585817, filed 1 June 2000, and is a continuation-in-part of 09/580,015, filed 26 May 2000, and claims benefit of provisional application 60/137010, filed 1 June 1999.

Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention.

There is no disclosure or contemplation of administration of antibodies which bind to synuclein-NAC in application 09/580,015. Provisional application 60/137,010 discloses methods of administering antibodies that bind to amyloid components for treatment or prevention of amyloid diseases (p. 6 lines 14 – 19). Amyloid diseases are defined to include Alzheimer's disease (see for example '010 application p. 16 line 31 – p. 17 line 12), and the provisional application clearly contemplated synuclein-NAC as an amyloid component (see p. 9 lines 23 – 25 and p. 17 line 13 – 16). The provisional application discloses methods of administering antibodies against synuclein-NAC for treatment of amyloid diseases (see claims 33 and 39). Thus priority is granted to 1 June 1999.

Rejections Withdrawn

4. The following rejections made in the previous office action are withdrawn:

A) The rejection of claims 11, 58, and 74 – 81 under 35 USC 112, first paragraph for lacking written description is withdrawn in light of the amendments.

B) The rejections under 35 USC 103 are withdrawn. Applicant is correct; neither Schenk reference is prior art.

Rejections and Objections Necessitated by Amendment

Claim Objections

5. Claims 11, 58, and 74 – 81 are objected to because of the following informalities: the claims recite "a NAC fragment", however NAC fragment is a very specific fragment of alpha-synuclein; it is well-known in the art to be residues 61 – 95 of alpha-synuclein (see Weinreb et al. 1996. Biochemistry 35:13709-13715, particularly Figure 1); the specific sequence is set forth in Masliah (WO 95/06407; of record) as SEQ ID NO:3 (see Masliah p. 96 line 5). Amendment to "the NAC fragment" is required. Furthermore recitation of the indefinitie article "a" when referring to this fragment encompasses any portion of the sequence. Appropriate correction is required.

Rejections Maintained

Claim Rejections - 35 USC § 112

6. Claims 11, 58, and 74 – 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of chimeric, humanized, or human antibodies which specifically bind to the non-amyloid component of alpha synuclein and chimeric, humanized, or human antibodies which bind to an epitope within residues 1 – 28 of A-beta, does not reasonably provide enablement for therapeutic or prophylactic treatment of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons set forth in the previous office action and explained in further detail herein. On p. 5 of the remarks filed 21 February 2006, applicant refers to the declaration by Dr. Koller in support of the enablement of the instantly-claimed invention. The declaration has been fully considered but is not persuasive. Dr. Koller's declaration is on point to administration of beta-amyloid peptide. The clinical trials referred to therein both used AN1792, which is a 42 amino-acid peptide (declaration, paragraph 2). The patients in the clinical trial who received the AN1792 developed antibodies against A-beta. However the declaration is not on point for two reasons. First, no antibodies were administered to the patients; the pending claims all require administration of antibodies, which are not the same as peptides. Antibodies have different structures, effects, and functions than proteins. Second, the declaration is only on point to A-beta. There is no mention of the NAC fragment of alpha synuclein, nor is there mention of antibodies to this peptide. In fact, the conclusion set forth in paragraph 9 of the Koller declaration is only on point to AN1792, and does not even try to extrapolate to other plaque components such as NAC. Thus the declaration submitted by Dr.

Koller is not sufficient to show that antibodies against NAC are able to prophylactically treat the disease, as recited in the claims.

Neither the specification nor the declaration submitted provide evidence of treatment of humans or animals with antibodies which bind specifically to NAC. The specification provides an example in which antibodies which bind NAC are able to reduce plaques ex vivo (see p. 115 of the specification, as well as previous office action, p. 4). As set forth previously, this is not a reliable model of Alzheimer's disease. Applicant argues, on pp. 5 – 6 of the remarks, that in the case of A-beta, the ex vivo results closely track those of the in vivo results and thus the ex vivo model should be considered an appropriate model for in vivo therapeutic and prophylactic treatment of Alzheimer's disease. The examiner disagrees. The article by Dodart et al. (2002. Nature Neuroscience 5:452-457, cited by applicant on IDS filed 21 February 2006) teaches that the ability to remove plaques from the brain is divorced from cognitive improvements. Dodart teaches that monoclonal antibody m266 reverses memory deficits in two tasks in mice, but has no effect on the amount of A-beta in the brain (see abstract, as well as Figure 1). This antibody is well-known to bind to residues 13 – 28 of A-beta (see for example Johnson-Wood et al. 1997. Proc Natl Acad Sci USA 94:1550-1557, especially Figure 1). Thus the findings of Dodart indicate that whether or not an antibody reduces the number of plaques in brain tissue is not relevant to the antibody's ability to treat the symptoms of Alzheimer's disease. Therefore the ex vivo model presented on p. 115 of the instant specification cannot be considered an enabling disclosure of treatment of Alzheimer's by administration of antibodies against NAC.

Applicant cites *In re Brana* and argues that the situation in *Brana* is analogous to the present case, and therefore the PTO should accept the ex vivo data as evidence of an enabling disclosure. The facts in *Brana* differ importantly from the instant case. In *Brana*, there was an in vitro assay which was predictive of the utility of in vivo compounds. Here, the in vivo work by Dodart indicates that the mechanism under study in the ex vivo assay, namely the ability to clear amyloid plaques, is not correlated with treatment of Alzheimer's disease. Because the ex vivo assay disclosed in the specification is not reasonably predictive of treatment of Alzheimer's disease, the case is not sufficiently analogous to *Brana*.

Applicant also argues that the full scope of the claimed invention is enabled, because even though complete prevention of Alzheimer's might not be enabled by the instant specification, this does not preclude the inclusion of prophylaxis in the claims, as not every embodiment of a generic claim need be enabled. Applicant appears to be arguing that claims

which encompass both treatment and prophylaxis should be considered enabling even if complete prevention is not enabled. While it is of course true that generic claims can include certain non-enabled embodiments, in the instant case claims 11 and 74 – 77 are drawn to treatment only and do not recite prophylaxis. However claim 58 explicitly recites "a method of prophylactically treating a patient"; of course this recitation and the concluding clause of the claim "thereby effecting prophylaxis of the patient" also applies to dependent claims 78 – 81. These claims do not include treatment, as the patients to be selected are those who are susceptible to, i.e. do not yet have, Alzheimer's disease. Thus claims 58 and 78 – 81 encompass only non-enabled embodiments.

In light of the above remarks, the rejection stands for the reasons of record.

New Rejections

Claim Rejections - 35 USC § 103

7. Claims 11, 58, 74 – 75 and 78 – 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masliah (WO 95/06407, published 9 March 1995, of record), Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 11 December 2001), and Solomon (1996. Proc Natl Acad Sci USA 452-455).

Masliah teaches treatment of Alzheimer's disease by administration of antibodies which bind to NAC. For the sake of brevity, the teachings of Masliah will not be repeated here; applicant is referred to p. 6 of the previous office action; the Masliah reference teaches the administration of NAC antibodies recited in claims 11, 58, 74 – 75, and 78 – 79. However Masliah does not teach administration of chimeric, humanized, or human antibodies which bind to an epitope within residues 1 – 28 of A-beta.

Becker teaches administration of antibodies which bind to A-beta for treatment of Alzheimer's disease (see column 7 lines 44 – 52). Becker's antibodies include fragments of antibodies such as Fab and Fab', as well as chimeric and humanized antibodies (see column 5 lines 50 – 58). Becker also teaches pharmaceutical compositions comprising the antibodies and methods of administering the antibodies to patients including via the intravenous route (see column 8 lines 19 – 42). Becker teaches antibodies which bind to the antibodies in beta-sheet conformation (column 7 lines 25 – 31), however Becker does not teach antibodies which bind to an epitope within residues 1 – 28 of the molecule, as specifically recited in the claims.

Solomon teaches that monoclonal antibodies which bind to residues 8 – 17 and 1 – 28, which are named 6F/3D and AMY-33 respectively, are able to inhibit aggregation of A-beta into

its toxic aggregated forms (see Results, particularly the paragraph spanning pp. 453 – 454). The reference teaches that these antibodies are particularly effective because they bind to those epitopes responsible for aggregation. Furthermore Solomon teaches suggests that these antibodies should be used for treatment of Alzheimer's disease (see p. 454, final two paragraphs).

It would have been obvious to one of ordinary skill in the art to co-administer antibodies which bind to the NAC component of alpha-synuclein, as taught by Masliah, and antibodies which bind to an epitope within residues 1 – 28 of A-beta, for treatment and prophylaxis of Alzheimer's disease, with a reasonable expectation of success. Becker teaches administration of anti-A-beta antibodies generally, and Solomon guides the artisan in selecting those antibodies which bind to epitopes within residues 1 – 28 of the molecule. Co-administration of two compounds each known to be effective for the same purpose is *prima facie* obvious and flows logically from the prior art. See MPEP § 2144.06.

8. Claims 77 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masliah, Becker, and Solomon as applied to claims 11, 58, 74 – 75, and 78 – 79 above, and further in view of Sabel (U.S. Patent 4,883,666, issued 28 November 1989).

The reasons why Masliah, Becker, and Solomon render obvious the invention of claims 11, 58, 74 – 75, and 78 – 79 are set forth above. None of Masliah, Becker or Solomon teach sustained release compositions for administration of the antibodies. Sabel teaches implantation of controlled release systems for treatment of neurological diseases (see column 10 - column 12). Sabel teaches the implants are suitable for administration to patients with Alzheimer's disease (column 5 lines 5 - 26). It would have been obvious to one of ordinary skill in the art to implant a controlled release system to administer the antibodies, as taught by Sabel, with a reasonable expectation of success. Sabel teaches there are many advantages to implantation of controlled release systems, including constant predictable release and local administration, thereby obviating the need for high systemic doses (see column 2 lines 49 - 65).

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON TURNER, PH.D.
PRIMARY EXAMINER

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3-29-06

Daniel E. Kolker, Ph.D.
March 24, 2006